

## **REMARKS**

Reconsideration of the subject application in view of the following remarks is respectfully requested. Claims 1, 7-9, 14, 15, 19-30 remain pending in this application. By this amendment, Claims 1, 9, 15, 19, 20, 23 and 27 have been amended. No new matter has been added to the subject application by this amendment, nor have any new issues been raised. Applicants reserve the right to pursue patent protection for any subject matter covered by the claims as presented prior to this amendment in this application or another application claiming priority from the present application.

### **Status of Application and Claims**

In the outstanding Office Action dated June 17, 2004, the Examiner acknowledged Applicants' request for continued examination and withdrew the finality of the previous Office Action dated September 17, 2003. The outstanding Action claims to be responsive to Applicant's Amendment and Response after final rejection filed on April 15, 2004.

In the outstanding Action, Claims 27-30 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 1, 9, 14-15, 19-23, 26-27 and 30 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over U.S. Patent No. 5,635,204 to Gevirtz et al (hereinafter referred to as "Gevirtz"), in view of U.S. Patent No. 5,840,731 to Nelson et al. (hereinafter referred to as "Nelson"), and in view of U.S. Patent No. 6,261,582 to Needham et al. (hereinafter referred to as "Needham"), and in view of U.S. Patent No. 5,891,885 to Caruso (hereinafter referred to as "Caruso"). Claims 7-8, 24-25, 28-29 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Gevirtz in view of Nelson, Needham, Caruso and in further view of Kaneko et al (Anesthesiology '94).

### **Response by Applicant**

Applicants traverse the Examiner's rejections primarily because of the reasons set forth herein below. Applicants believe the claims as examined are directed to subject matter which is neither taught nor suggested by the cited references. By this amendment, Applicants have amended claims 1, 9, 15, 19, 20, 23 and 27 in an effort to advance prosecution, but not in acquiescence of any rejection thereto. Applicants respectfully submit that the claims as now presented are also directed to subject matter which is neither taught nor suggested by the cited references. Furthermore, Applicants believe these claims are now in condition for allowance. For illustrative purposes, Applicants have addressed the rejections in the outstanding office action as if the rejections had been asserted against the claims presented herein.

### **Claim rejection — 35 U.S.C. § 112**

Applicants have amended Claim 27 to obviate the 112 rejections, and in particular, to claim the subject matter contained in the specification in such a way as to enable one skilled in the art to make and/or use the present invention. Thus, withdrawal of this rejection is respectfully requested.

### **Claim Rejections – 35 U.S.C. § 103**

With regard to the 103 rejections, Applicants believe that the burden necessary for establishing a *prima facie* case of obviousness has not been established.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner alleges that the instant invention and Gervitz both teach a composition comprising an NMDA receptor antagonist (ketamine), an analgesic (fentanyl) and an excipient/carrier (polyisobutylene) and a method for applying the composition to the skin.

The Examiner alleges that Nelson and Needham disclose fentanyl and morphine as interchangeable and combinable analgesics. Applicants respectfully disagree and traverse the rejection.

A *prima facie* case of obviousness requires that three basic criteria be met, one of which is that there be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In the instant case, the Examiner has picked parts from several references to render a combination that renders Applicants' claims unpatentable, even though the Courts have made it clear that the teaching or suggestion to make the claimed combination, among other things, must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck, supra*.

The Examiner claims that it would have been obvious to substitute fentanyl for morphine in the Gervitz composition based on teachings in Nelson and Needham because of the expectation of producing similar analgesic effects via the opioid pain receptor.

Applicants disagree that the expectation of switching components to produce a similar effect, based on teachings of different compositions intended for unrelated uses, would provide sufficient motivation for one skilled in the art to practice Applicants' invention as now claimed.

Gervitz relates to a transdermal patch and does not teach or suggest topical application of pharmacological agents by an aqueous solution, gel, lotion, ointment, cream or spray. Nelson relates to a polymeric matrix device for administering analgesics and does not teach or suggest topical application of an analgesic by an aqueous solution, gel, lotion, ointment, cream or spray. Needham relates to a paste of an analgesic and microfibrillar collagen with a viscosity slightly less than that of toothpaste (see, *e.g.*, column 4, lines 16-17 of Needham; hereinafter “the Needham paste”), *i.e.*, the Needham paste is not an aqueous solution, gel, lotion, ointment, cream or spray. Furthermore, Needham does not teach or suggest the use of any excipients, let alone an aqueous or gel excipient.

Even assuming, *arguendo*, that the Needham paste relates to an aqueous solution, gel, lotion, ointment, cream or spray, the Needham paste is not a topical pharmaceutical composition nor is it applied topically. The Needham paste is applied to exposed nerves to provide pain release (see, *e.g.*, column 4, lines 1-4), *i.e.*, the Needham paste is not applied topically.

Applicants also respectfully point out that the polymeric matrix device of Nelson is implanted (see, *e.g.*, Abstract of Nelson), *i.e.*, it is also not a topical pharmaceutical composition nor is it applied topically. Furthermore, there is no teaching or suggestion in Gervitz to replace the transdermal patch with a paste. Lastly, Caruso does not cure the deficiencies of the proposed combination in terms of establishing a combination that can render Applicants' amended claims unpatentable. Thus, Applicants contend that a *prima facie* case of obviousness against the present invention as now claimed has not been established.

For example, amended Claim 1 is directed to a topical pharmaceutical composition that includes, *inter alia*, "a NMDA receptor antagonist in a tolerance-attenuating dosage, an analgesic that functions through an opiate receptor and a pharmaceutically acceptable topical excipient, wherein the dosage of NMDA receptor antagonist is within a tolerance-attenuating range sufficient to yield a dose-lowering effect on the analgesic such that the concentration of analgesic necessary to provide effective analgesia is within a range of about 1.0 to about 10% by weight of the composition."

Also, Claim 9 as amended is directed to a method of providing peripheral analgesia and not central or systemic analgesia to a mammal that includes, *inter alia*, "topically administering a tolerance-attenuating dose of ketamine prior to, concurrently with, or following topically administering morphine, wherein the morphine functions through a peripheral opiate receptor, wherein the administration is by topical application of an aqueous solution, gel, lotion, ointment, cream or spray and the dosage of NMDA receptor antagonist is within a tolerance-attenuating range sufficient to yield a dose-lowering effect on the analgesic such that the concentration of analgesic necessary to provide effective analgesia is within a range of about 1.0 to about 10% by weight of the composition."

It is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. Applicants respectfully submit that there is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Furthermore, systemic combinations of opioids and analgesics are non-analogous art, having no bearing on the function of topical compositions providing only localized effects in the periphery. As such, the skilled artisan working to develop a localized peripheral pain reliever and methods of its use is not motivated by literature describing systemic responses.

A *prima facie* case of obviousness requires that the prior art reference (or references when combined) teach or suggest all the claim limitations. As discussed above, the combination of references cited by the Examiner to support the rejection of the independent claims 1, 9, 15, 23 and 27 do not anticipate Applicants' presently claimed invention. Thus, the 103 rejections against these claims should be withdrawn.

With regard to dependent claims 7-8, 24-25, and 28-29, Kaneko does not cure the deficiencies of Gervitz, Nelson, Needham and Caruso. Specifically, Kaneko does not teach or suggest the use of any excipients, let alone an aqueous or gel excipient. Kaneko also does not teach or suggest the topical application of pharmacological agents by an aqueous solution, gel, lotion, ointment, cream or spray. Instead, Kaneko relates to epidural morphine injection (see, e.g., abstract and page 141 of Kaneko), which is a systemic, not a topical application. Since Kaneko does not cure the deficiencies of Gervitz, Nelson and Needham, the combination of Gervitz, Nelson, Needham and Kaneko do not render claims 7 and 8 obvious. Accordingly, Applicants respectfully request withdrawal of the rejection.

Applicants independent and dependent claims as amended are directed to subject matter that is not disclosed or suggested by the cited references, as discussed above, and therefore can not be rendered obvious by any hypothetical combination thereof.

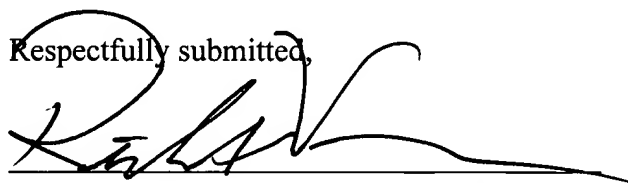
### **Conclusion**

A *prima facie* case has not been established. Thus, the 103 rejections are improper and must be withdrawn. Also, independent Claims 1, 9, 15, 23 and 27 as now presented contain limitations which are neither taught nor suggested by Gevirtz, Nelson, Needham, Caruso or Kaneko, either alone or combined. Furthermore, since the claims that depend from these independent claims provide further limitations thereto, the dependent claims, namely Claims 7-8, 14, 20-22, 24-25, 28-30, are also not rendered obvious by Gevirtz, Nelson, Needham, Caruso or Kaneko, either alone or combined. Accordingly, withdrawal of the 103 rejections is therefore respectfully requested. In addition, Applicants believe that the formal deficiencies have been addressed by this amendment and that the 112 rejections should therefore be withdrawn also.

It is respectfully submitted that as a result of this amendment and discussion relating thereto, all of the claims presently pending in this application are in condition for allowance, and such action is earnestly solicited.

If the Examiner believes that a personal or telephonic interview may facilitate resolution of any remaining matters, Applicant's representative may be contacted at the number indicated below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Richard H. Newman', with a long horizontal flourish extending to the right.

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